Non-IO in an IO World

Based on the Web Panel Discussion on January 26, 2017

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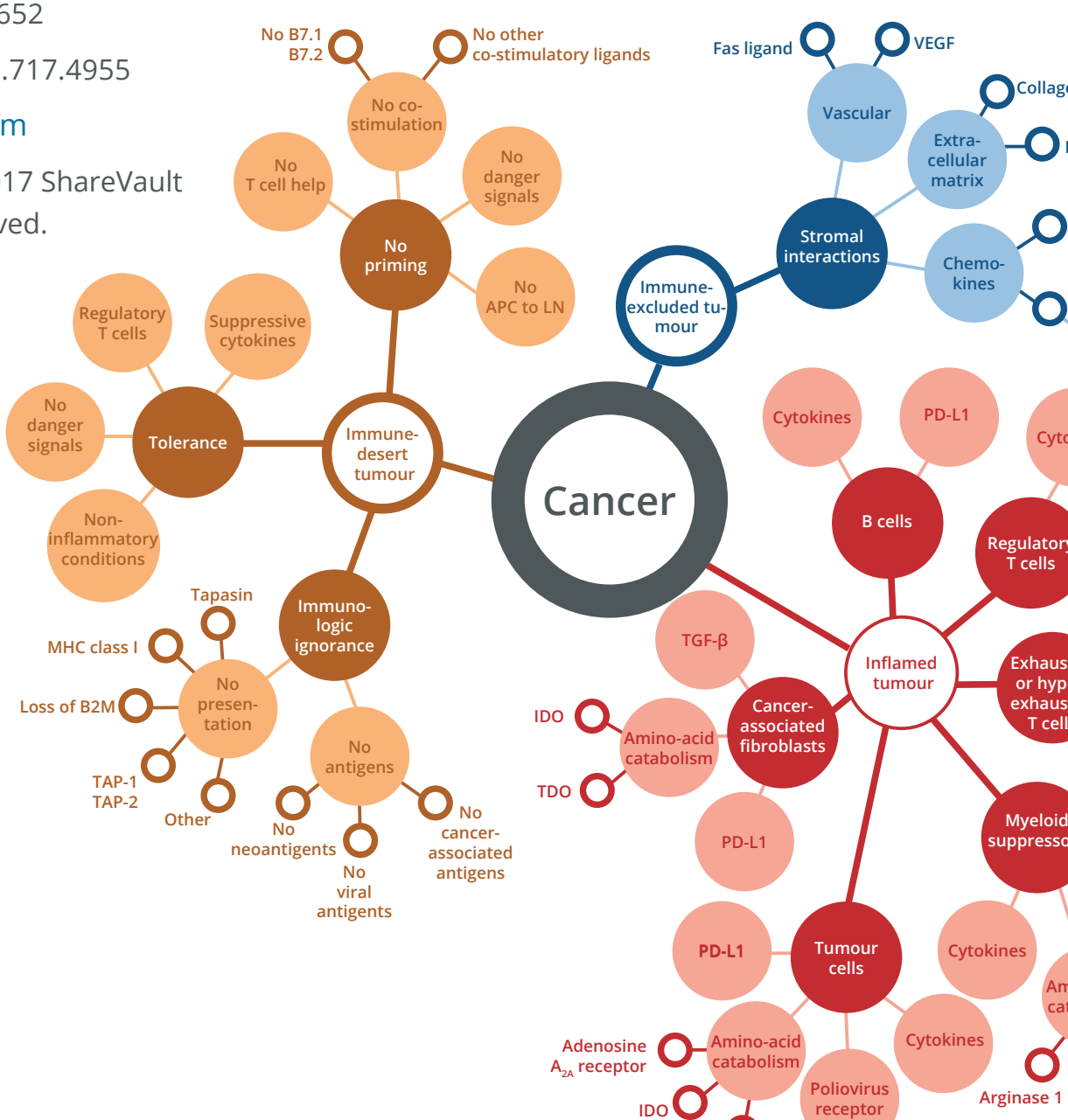


The recent clinical successes of checkpoint inhibitors have made immuno-oncology (IO) an amazingly hot area for pharmaceutical and biotech deal making. With checkpoint antibodies seen as backbones for combination therapy in cancer, many in oncology are wondering what the role of non-immuno-oncology (non-IO) agents will be in a world that is increasingly dominated by immuno-oncology therapies.

To find out, we assembled a panel of experts from global pharmaceutical companies, a leading academic cancer center, and a top business development consulting firm to find out whether they believe there will continue to be opportunities to partner non-IO agents and to discuss what role non-IO agents will play in oncology's future. The discussion took place on January 26th, 2017 and was moderated by Linda Pullan, a biotech licensing and pharmaceutical business development consultant.

LINDA PULLAN: **What is the balance of IO and non-IO today? Give us a sense of the numbers.**

JEFF BOCKMAN:

There's no doubt that immuno-therapies of one sort or another are on everyone's agenda. While IO assets are still a fraction of the overall oncology market, the growth in IO, mostly defined by checkpoint inhibitors, far outweighs that of non-IO cancer drugs. Total sales of IO assets by 2022 are expected to be $20B in the U.S. and $35B worldwide. In the U.S., the compound annual growth rate (CAGR) of IO products from 2012 to 2022 is projected to be 43%. However, it's important to remember that while IO agents are demonstrating very significant and unique types of activity, they are not the whole story.

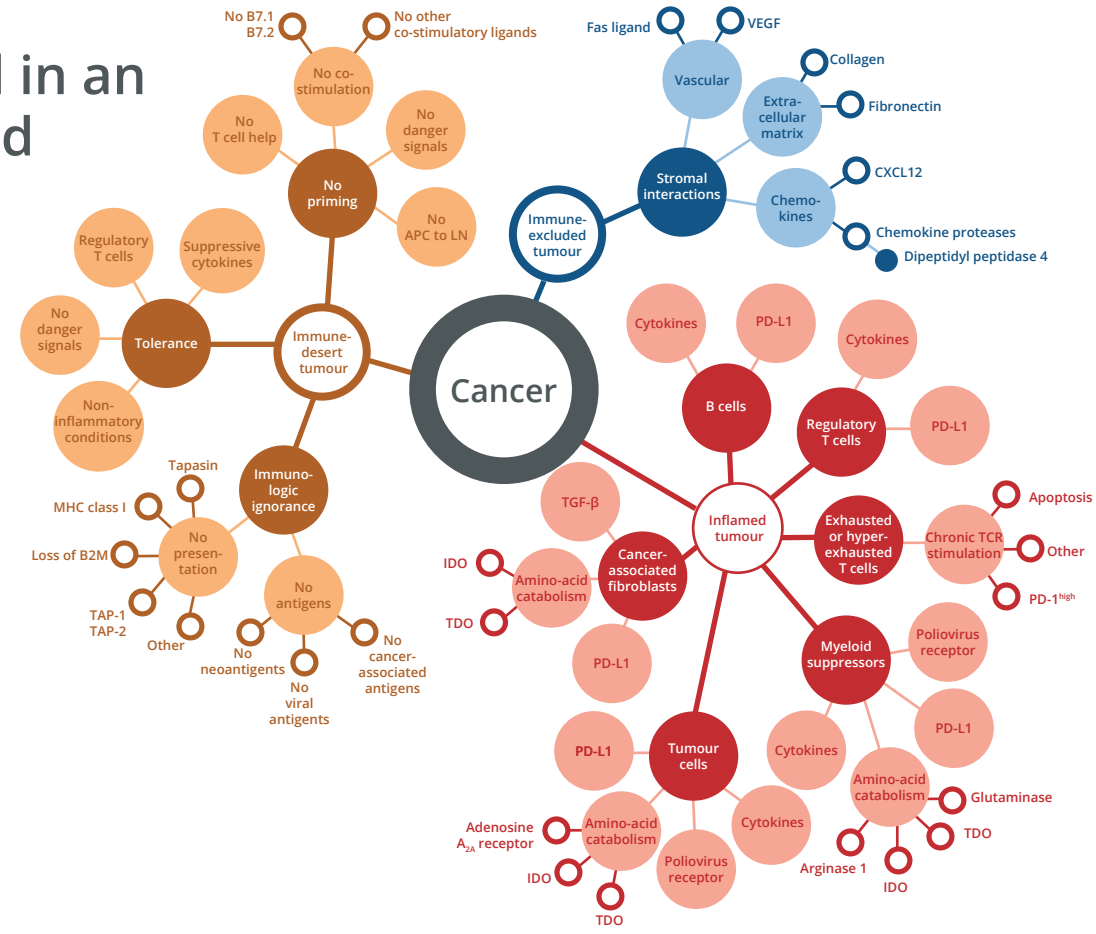
Within the oncology pipeline, non-IO and IO compounds are split by approximately 2/3 to 1/3, respectively (~1200 non-IO and ~550 IO agents).

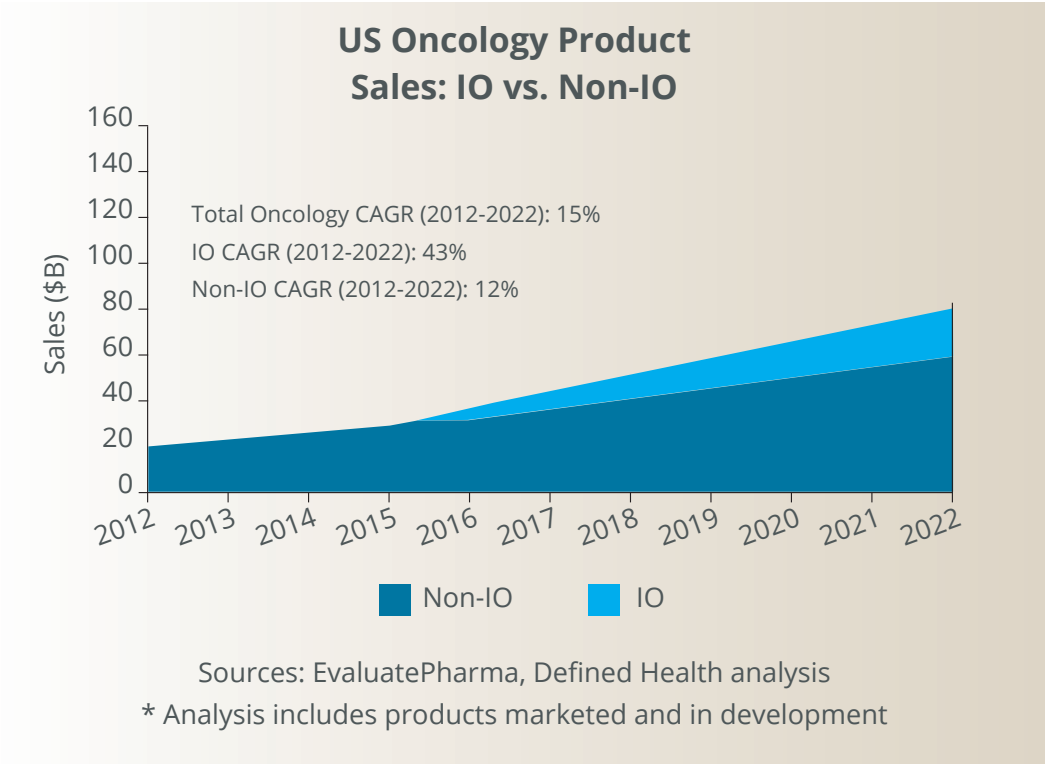
LINDA: **Are all large pharmaceutical companies investing in IO?**

JEFF:

A great majority of pharmaceutical organizations have invested in IO. Half a dozen or more pharmaceutical companies have made IO a top priority, and there are many others that have invested on a smaller level. If you define IO by checkpoint inhibitors, co-stimulatory agonist, vaccines, adoptive cell therapies, and some of the bispecifics, then I would say that **to varying degrees IO is being pursued by most of the top 20 pharmaceutical companies.**

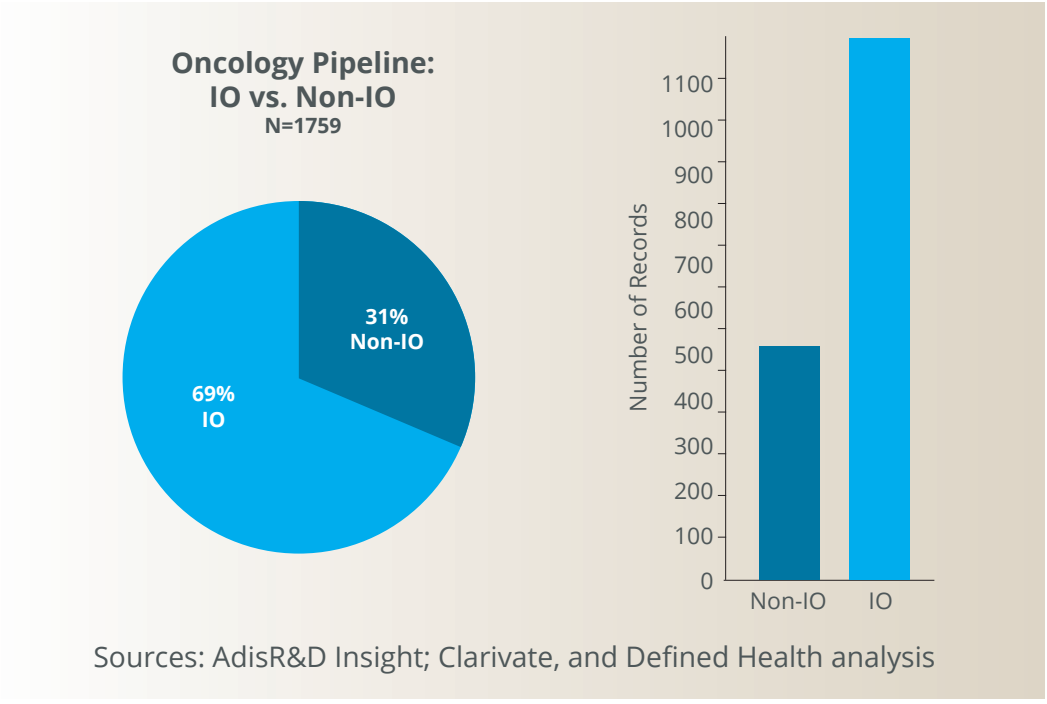
Non-IO Framed in an IO World





Sources: EvaluatePharma, Defined Health analysis
* Analysis includes products marketed and in development

When you look at the IO versus non-IO pipeline, you see that non-IO still dominates the pipeline, but that IO agents are making rapid inroads.



Sources: AdisR&D Insight; Clarivate, and Defined Health analysis

LINDA: How much of your research is focused on IO?

ERIC HAURA:

At Moffitt Cancer Center we've always had an active immunology program, but certainly the excitement lately has driven an increase in research within that program. We anticipate hiring a number of new faculty members to enhance our immunology program. This will include not only basic scientists, but also recruiting and building out more clinical programs. For instance, **we have an emerging team that is focused on clinical management of patients using CAR-T and other engineered T-cell products**, because we feel that that's going to require an expert team to manage patients during their hospitalization. We're also investing in our lung cancer group, both bringing in basic scientists and filling out more translational work related to immuno-oncology. This is a big area of interest and it's expanding.

AXEL HOOS:

When we partnered with Novartis two years ago, we divested our targeted therapy oncology business to them. What that left us with was a clean slate, enabling us to focus our oncology efforts on the areas of science that we felt were the most relevant. Our focus fell on immuno-oncology and cancer epigenetics. For us, immuno-oncology includes cell and gene therapy. Our cell and gene therapy efforts are ongoing. **The ratio of our focus is about 2/3 IO to 1/3 epigenetics**. We have chosen to be focused on those two areas because they already have a great deal of depth, so we don't feel the need to re-enter the targeted therapy space.

> **The ratio of our focus is about 2/3 IO to 1/3 epigenetics.**

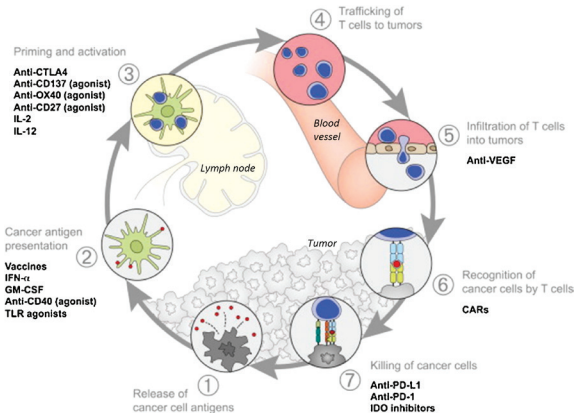
LINDA: What is today's thinking on backbones? Are they interchangeable? Is there checkpoint fatigue?

PETER SANDOR:

That's a question everyone wants an answer to. The backbones have definitely changed cancer treatment, which creates an issue for follow-on compounds from a development and strategy perspective. **It's really hard to define patient populations that are checkpoint inhibitor naïve.**

AXEL:

It's obvious that there are more conventional oncology targets, like chemotherapy, that are still backbones that we're adding onto, including IO agents. An example is treating lung cancer with chemotherapy combined with PD-1. Beyond that you will see that some of the established checkpoint modulators are becoming backbones, and people are either using them as a single agent or as a platform to add onto. That's what PD-1 and PDL are for. **The question becomes: What comes next? How strong of a backbone are these agents, and will there be others that either complement them or address other patient populations that are not covered by these backbones?** We have not yet cured everyone. We've seen great efficacies and enhancements of existing therapies and improvement of survival and long-term responses, but we have not yet made that benefit available to every patient. There are still large gaps to be filled. In order to fill those gaps we need to look at alternative mechanisms in the IO space, and those mechanisms will likely offer the opportunity to establish parallel backbones to the ones we are seeing emerge now.

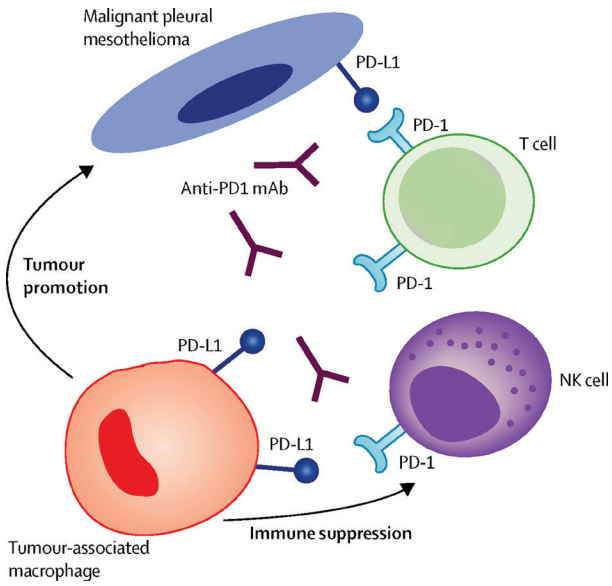


JEFF:

The recent approval data on checkpoint plus chemo and lung cancer should be considered a significant sea change because there is very strong data for the checkpoint as an alternative to a chemo backbone. In melanoma, we saw a paradigm shift from BRAF and MEK inhibitors, which had poor durability, to checkpoint inhibitors, and in various cancers now checkpoint inhibitors combined with "targeted agents."

In the past, targeted agents (whether antibodies or tyrosine kinase inhibitors) were combined in the hope that they could obviate the need for conventional cytoreductive cytotoxic chemo. That never quite happened. However, in a few rare cases we're starting to see glimmers of that now with IO agents. That is not to say that we're heading to a world where we're going to see an IO doublet or triplet combination right out of the gate. **There may not be enough extra value to justify adding those checkpoints on top of first-line agents that already lead to fast, direct tumor cell killing and control of responsive tumors.**

But importantly, an enabling combination of IO, in the appropriate type of cells, may help unleash the various types of antigens that the immune system will be able to enact upon once it is de-repressed in one form or another, and perhaps when further stimulated by the next wave of the IO antibodies or co-stimulatory agonists.

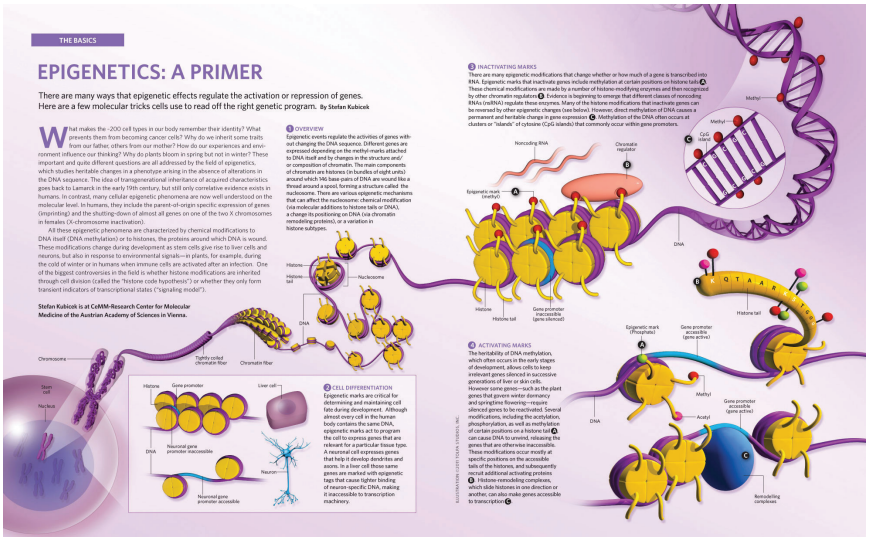


Right: From "Immune checkpoint inhibitors in malignant pleural mesothelioma" in *The Lancet*, May 2017.

LINDA: **Where are the non-IO opportunities? Are you seeking to license any non-IO assets? Perhaps in epigenetics?**

AXEL:

At GSK we've established a very focused approach to certain areas of science. There is a bit of a targeted therapy flavor to the epigenetic space at the moment. Right now we're still **identifying patient populations on the basis of mutations in epigenetically relevant genes**. That's the trend that is clear and is reminiscent of targeted therapies. We do have an interest in epigenetic compounds and we're certainly active in that area. Relatively speaking, this is a smaller area in terms of the number of technologies out there. But our focus is more on IO than on epigenetics. We have definitely decided not to re-enter the targeted therapies arena.



PETER:

At Astellas we're looking for clinical benefits as well as looking at those areas where there are commercial benefits. Primarily it's about understanding the biology and understanding the benefits that these programs can bring to the patients. We're looking for assets with clear clinical benefits.

LINDA: Looking at the pembro plus chemo data, how do you see that data shaking up management of lung cancer?

PETER:

The question is, are you achieving a benefit from adding agents together as a result of some molecular synergy or are you achieving a benefit as a result of mimicking the sequential addition of drugs? The concern I have is, while some of these clinical trials may show strong outcomes as a result of combining drugs, we do have to deal with the real patients we see in clinic and not all of them are clinical trial candidates. **So I wonder if because of issues of toxicity, we are still going to be using agents in a sequential way?** For some patients, we may feel the need to lump all the drugs together, because patients are in crisis, but in other cases, because of quality of life issues or other more real-world issues, we may need to begin our therapy on a simple path and realize that we can sequentially dose drugs to achieve positive outcomes in patients.

LINDA: Do non-IO targets play a role in permitting IO to function?

PETER:

If you look at the clinical benefit a patient can derive from a treatment, in some cases patients see a better response from combinations. But there are different approaches not limited to permitting IO to function, where **non-IO or IO products can be differentiated in a defined patient population or differentiated on their own against the checkpoint inhibitor**. So, these are significant assumptions to consider in product evaluations.

> **Non-IO or IO products can be differentiated in a defined patient population or differentiated on their own against the checkpoint inhibitor.**

LINDA: Are there indications or mechanisms for which IO combinations will never be important?

ERIC:

I wouldn't say never, but there are examples where IO combinations may be less important. We do take care of patients who were never smokers and now have lung cancer. Some of this population have genomic alterations in receptor tyrosine kinases. A good example is ALK. The research and understanding of why patients become resistant to ALK inhibitors has really moved quite quickly. We now understand secondary mutations and how they may match up with additional kinase inhibitors. In my practice, while we have opportunities for IO therapies, for example with patients that have relapsed on Crizotinib, I'm more inclined to employ re-biopsies and analysis of mutations to get a better sense of why patients become resistant to targeted agents like ALK inhibitors. **For some select diseases, I think the field will focus on interrogating tumors and looking for continued targeted agents.** Of course, there will be some patients that are going to escape targeted agents through mechanisms that can't be controlled anymore, which is when IO will be used opportunistically.

LINDA: Is the checkpoint lack of access to brain metastasis important to you in your practice?

ERIC:

Yes, that's actually becoming an emerging problem for us in targeted agent therapy as well. Both melanoma and lung cancers are definitely escaping through the sanctuary system of the nervous system. This is an area of emerging research for our melanoma group. From a practical point of view,

it is really going to require multiple modality therapy with radiation oncologists and surgeons, because there are ways to get at these tumors, but **understanding how the brain may protect against either immunological agents or targeted agents is going to have increasing importance.** This is because we're seeing people who are essentially controlled with their disease systemically, but have relapse in the brain, which can become problematic or potentially lethal.

Understanding how the brain may protect against either immunological agents or targeted agents is going to have increasing importance.

PETER:

Given the prior history of checkpoint inhibitors in prostate cancer, that's definitely an intriguing signal that sequence does matter.

JEFF:

That's an excellent point, because we don't always know initially what the physiologic or biologic synergy is in those combinations. Take the example of myeloma, where the first trials with checkpoints alone saw minimal activity and we thought that checkpoints weren't going to work. And, low and behold, you add an IMID such as Revlimid and you have very significant outcomes. That speaks to the value of non-IO agents. At the end of the day, **many, or all, of these non-IO agents draw much of their clinical benefit from how they engage the immune system, either directly or indirectly**, whether it's a chemo agent or a TKI, etc.

AXEL:

Addressing this in the brain or in other parts of the body with immuno-oncology agents, particularly checkpoint modulators, should be done in a very systematic manner. It should be very context dependent and not dependent on approaches for all patients. It will depend on very specific attributes for individual patients, where the immune state or other parameters are relevant for driving the growth of the disease or driving the ability of checkpoint modulators to change it. For example, we started out with ipilimumab (the CTLA-4 antibody) and saw activity in the brain. The immune system is able to send itself into any part of the body, including the brain. There have been studies done with CTLA-4 that indicated very clearly in melanoma patients that in the brain, the immune system can respond and intervene. **The context matters for complete activity of these agents.** We've seen in colorectal cancer that there was no activity for some time with PD-1, but once we identified microsatellite instability or mutation load as a factor, we started seeing significant activity.

Similar things are true in malignant melanoma—modest activity with PD-1 alone, but in combination we see a 70 to 80 percent response rate. So, it's very context dependent. I'm convinced that with the right immune intervention, the universal defense mechanism that the immune system represents, which is extremely potent, can be directed against any disease. You just have to figure it out in context. In the targeted therapy space we are beginning to very carefully define patient populations where certain interventions or agents matter. I think we will see some of that in IO. **Once we identify the right setting for the right intervention, we'll see striking activity with IO in almost all settings.** But there's going to be a lot of variability, and it will take us some time to figure it out.

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JEFF:

The context of each individual patient is very critical. We can determine that context in multiple ways, including diagnostic/prognostic systems and signatures, such as Nanostring DNA, RNA and protein immune profiling and other ways. It's a powerful concept, and it's reflected in the new update from the Chen and Mellman paper in *Nature*, where it is posited that **the immune set point is not a set point that is going to be common across everyone or even across all tumors; it's going to be individualized**. It's important to develop a personal context of an individual's immune system and their particular cancer and the interplay between them. **Everything they've gone through in life could end up being relevant to their immune set point, including their microbiome.**

PETER:

Which raises the question: How possible is it to get to a point where you can test each patient individually and be able to tailor the therapy for very different mechanisms for each individual patient?

Everything they've gone through in life could end up being relevant to their immune set point, including their microbiome.

JEFF:

I'm not saying that we'll have a unique product for a unique patient, but we may benefit, as the pipeline certainly shows us, from a large array of options. Not all patients will benefit from the same agents. That's why context is so important.

AXEL:

Context is very important. **We have seen non-IO agents become IO agents as we understand what they do to the immune system**. That can lead to combinations that are meaningful or to identifying a disease state or an immunological state for a patient that enables an IO therapy to

work better. I think **we will see patient populations defined not only by what agent they received, but also what that agent did to their immune state**. This is one of the elements that will likely drive the success of IO.

LINDA: How important is it to temporarily separate the effects of non-IO therapies on suppressing the immune system for subsequent immune responses?

ERIC:

That's something that we haven't done a great job at in oncology. Oncology clinical medicine uses a sequence of drugs, so we tend to be hyper focused on first line, second line, third line treatments, but how different mechanisms were sequenced is perceived as less important and infrequently tracked.

A lot of signal transduction inhibitors are probably inhibiting signal transduction in immune cells, and we have to be very careful about the potential timing of how those agents were used and how they remodeled the immune system before we bring in new agents. Similarly, epigenetic drugs can really reshape gene expression and potentially reactivate genes. Then you can introduce IO. Some of us are trying to leverage epigenetics to help IO work better. This is a major area that oncology can

benefit from. We spend a lot of time giving people therapy on an every three week basis or putting pills in people's mouths and just saying take it every day until you get worse, but not thinking if they need it every day or if they can take breaks or whether we can sequence targeted agents in a better way. **Can we take advantage of evolutionary theory to time the delivery of therapeutics better?** There's been interesting work in how to sequence targeted agents with standard, old-fashioned DNA damaging drugs, which could really change therapy for patients. This is an area that needs more attention.

JEFF:

We're learning constantly. Remember, in the early days of IO, lung cancer was not high on the list of cancers that people would have said would be immuno-responsive. We have a whole different viewpoint now. Similarly, immuno-suppressive "chemo agents" may be immuno-suppressive in some ways, but that may not be broadly true. Some of those agents may repress some of the bad actors, like Tregs or myeloid-derived suppressor cells. Not to mention that some chemo can lead to immunogenic cell death. Five years ago many of us believed that combining a taxane, which is myeloid suppressive, with an IO agent would probably not work very well. The thought was that it would be risky because you would be suppressing the immune system and thereby counteract what you're trying to do with the IO agent. That combination now has approval. Abraxane is also going in combination in pancreatic with checkpoints. Also Gemcitabine has beneficial immuno-modulating activity. So, the immune impact of chemo is not obvious. I think **broadly labeling chemo as being immuno-suppressive and therefore countering the benefit of an IO agent is not a blanket statement you can make.** It's dependent on drug, on context, on sequencing and timing of the relative use of those agents, etc. modulating activity.

LINDA: What about combinations used to debulk tumors followed by an IO agent to clean up cancer stem cells?

AXEL:

I would say it's a form of prior therapy. I wouldn't see it as a combination approach. Debulking creates an environment that is then more amenable to IO intervention. Depending on what you use to debulk, you might have a very potent immunological effect. The immune system may be just a clearing mechanism, but we have seen that it can be more than that. There are areas emerging where you can use chemotherapy as an immune clearing mechanism, so **you can actually deplete an emerging immune system and allow a new, and much more sensitive, immune system to emerge.**

We see this with the induction regimen for the cell and gene therapy approaches. These approaches, even though we're infusing highly potent cells, don't work alone; they need preconditioning chemotherapy. That sets the stage for the immune system to be ready to exert its effect. That's one example. Another is, **instead of combination therapy, you use the concept of priming the immune system and then follow that with a maintenance therapy approach**. It's a different development strategy, but it enables IO agents to find their place without having to look for combination toxicity.

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LINDA: Let's talk about specific approaches. Is supportive care even less important in an IO world? Will there by supportive care for cytokine release syndrome?

JEFF:

We're already seeing this for dealing with side effects of adoptive cell therapies, such as the application of anti-IL-6 agents that were originally developed for immune inflammatory disorders. So, there are drugs to manage some of the cytokine storm effects that are seen. More broadly we could ask whether IO agents are a panacea that are all efficacy with zero AEs. The answer is, no. In fact, as exemplified by the article in *The New York Times* in December, it's becoming more apparent to more people as more IO drugs are available in more settings and more patients are exposed to them, that there are adverse events, some manageable, some less manageable.

The short answer is that **there are going to be new opportunities for management of the specific immune-related adverse events** that we'll see, not just with the mono-therapies in this first generation, and not just with CTLA-4, which is the only formal combination we have right now, but with the other co-stims and combinations of checkpoints with oncolytic viruses like Imlygic, etc.

LINDA: Does IO change your thinking on prevention?

ERIC:

Yes, I think so. It's interesting to think in the context of lung cancer prevention, if you understand the early genetics of cancer and the early involvement of preneoplastic tumor cells with the immune system. If you had a better understanding of that biology, and you could match that with therapeutics in a high-risk population, I think this could be very important. From the practical side, when we look at prevention, we have to pay careful attention to the toxicity and the tolerability issues. Right now, it's worrisome to use checkpoint inhibitors

on healthy patients, but at the same time I think **it's a natural move forward to ask what we should be doing for modulating the immune system as a preventative strategy**.

LINDA: Has IO changed the balance of hematological versus solid tumors?

AXEL:

We have been incredulous toward certain concepts for some time. At first we didn't think immuno-therapy would work. I think we're over that one. Then we developed the concept that hematological malignancies would NOT be amenable to immunological intervention. That was a misconception. If you look at bone marrow transplantation and the way it exerts its effects, it has to be defined as an immuno-therapy. Even though there is chemotherapy involved, the actual effect is immunological in nature.

I don't see why hematological malignancies should be an exception. There are already certain interventions that work there very well. In Hodgkin's lymphoma we've seen very high response rates with PD-1, just as a monotherapy. We've seen that heme malignancies can be treated with immuno-therapy. We've seen genetically engineered T-cells that work in CD19 positive T-cell malignancies. We've seen BCMA CAR-Ts emerge for certain types of myeloma. And, depending on the targets we can utilize, I think **we will see efficacy in other types of liquid tumors. Just give this some time; it's still very young as an investigative area** within the immuno modalities of IO. But I think both solid and liquid tumors are amenable to the modalities of IO.

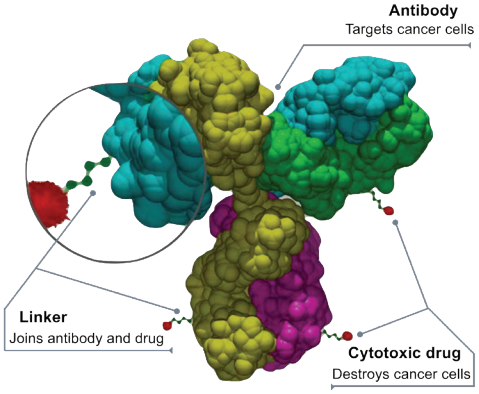
LINDA: Is there a future for new cytotoxics and antibody drug conjugants (ADCs)?

ERIC:

I think so. We often get fixated on concepts that we subsequently prove are untrue. And I think we have to be wary of a herd mentality, where everyone is so fascinated with IO therapy that we give up other things. Certainly targeted therapy for lung cancer has been a major concept over the last ten years. We're very fortunate that people were working on immunology and immuno-oncology for lung cancer because they're the ones that led these new breakthroughs.

So, in terms of ADCs, there's interesting data on targeting DLL3 in small cell lung cancer, which has seen no benefit from targeted agents in the last couple of decades. My sense is that all the genomic and proteomic atlases of cancer that are emerging are going to provide interesting targets. **By studying tumors serially through therapeutic trajectories we will uncover new targets that are going to be important and new technologies to build those ADCs.**

I think new cytotoxics could be interesting, but I think they need to be led by mechanism of disease. I think general drugs that are screened and have efficacy in cells or models, without fully understanding the mechanism and how it fits into a therapeutic landscape, may see less enthusiasm.



AXEL:

I think the ADC story is still unfolding. There are a lot of ADC programs in the clinic, and we will see what they can do. There are basically two major aspects to any ADC. One is the poison that we are using and then, of course, the target. If you choose BCMA as the target, and if you attach an auristatin derivative

you can actually achieve more than a sixty percent response rate in therapy refractory multiple myeloma. So, ADCs can be effective if you target the right target and get the substance that kills the cell to the right place.

LINDA: Are you interested in drugs that are aiming at mechanisms of resistance to tyrosine kinase inhibitors (TKIs)?

PETER:

That's definitely a large problem for people who receive kinase inhibitors. So, the answer is, definitely yes. The challenge is the evolution of pathway mutations and finding the different sequences and combinations of drugs most likely to work. I think a big question will be whether, in some cases, immunological mechanisms and kinase inhibitors can deliver high response rates and long-lasting responses.

LINDA: What about cancer stem cells interests you?

AXEL:

The cancer stem cell story is still undecided. There have been a lot of clinical investigations and a lot of work has been done. I haven't seen a big success yet. I've never been a believer in the cancer stem cell concept the way it has been outlined. **We need a randomized clinical trial that shows us that the stem cell pathway can deliver a major benefit**. If we get there, then that field might actually begin contributing to new standards of care, but I haven't seen it yet. I would like to see that succeed, but it's an area that's still undecided.

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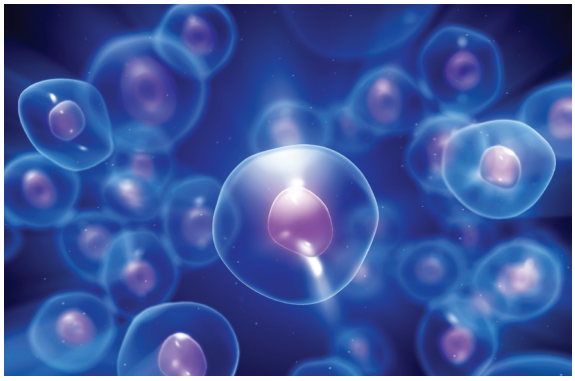
JEFF:



I agree from the standpoint of clinical validation. There are cancer settings where there's much stronger data for the presence of the cancer stem cells. However, I think **the important distinction is between the potential existence of a stem cell that can recapitulate the primary tumor and its importance for dormancy or, ultimately, for seeding or reseeding the growth of the tumor**. Then, there are also the practical implications of how you target and what you would accomplish by targeting it. If we could target early and prevent spread, that would be great, although in most cases cancers are diagnosed pretty late. It could mean that we have to develop these in some type of a maintenance setting or something that prevents recurrence or relapse at the same time, hopefully where you're addressing the bulk tumor cells.

There's no doubt that we're talking about something that is very heterogeneous, but there are certainly any number of companies that are working on cancer stem cells. Unfortunately the data to date have not been stellar, at least clinically, for those that claim to have either purer cancer stem cell targets or targets that are expressed both on cancer stem cells and on bulk tumor cells.

LINDA: The thinking on cancer metabolism has changed in relationship to IO. How so?

ERIC:

We've known for a hundred years or so about the alteration in cancer cells being different in terms of how they rewire metabolism. One could argue that early cytotoxic agents and chemotherapy drugs work through metabolic pathways.

This is an area we've seen interest in some companies and some academia, and maybe in some ways IO stalled out the interest in cancer metabolism. I think what we'll see instead is **looking for synergistic opportunities where we're able to target metabolic pathways in T-cells** that are important in tumor control.

We may see clever ways in which that will be either sequenced with immuno-therapy or combined with immuno-therapy. It's certainly a very interesting area. Looking at ways to target glucose transporters and understanding the importance of those targets both in tumors, but more importantly, the importance of those targets in normal host organs will be critical to avoid potential side effects.

JEFF: Which is why you see many people referring to metabolism now as **immuno-metabolism.**

LINDA: Has IO changed the thinking of the attractiveness of various modalities including everything from gene editing to drug delivery?

AXEL:

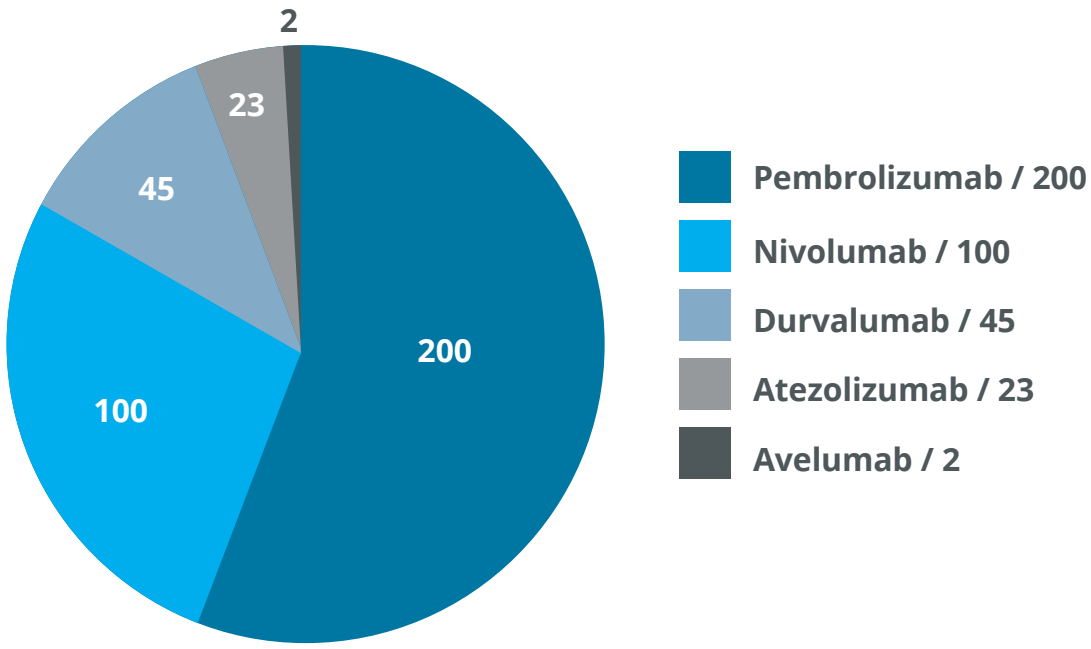
IO has clearly changed thinking on modalities. Certainly with cell and gene therapy we're seeing successes, although we have to remember that this space is still young. Immuno-oncology has been changing the perspective quite substantially.

LINDA: In light of the number of clinical trials utilizing PD-1s in combination, how do you stand out from the noise if you have a non-IO asset?

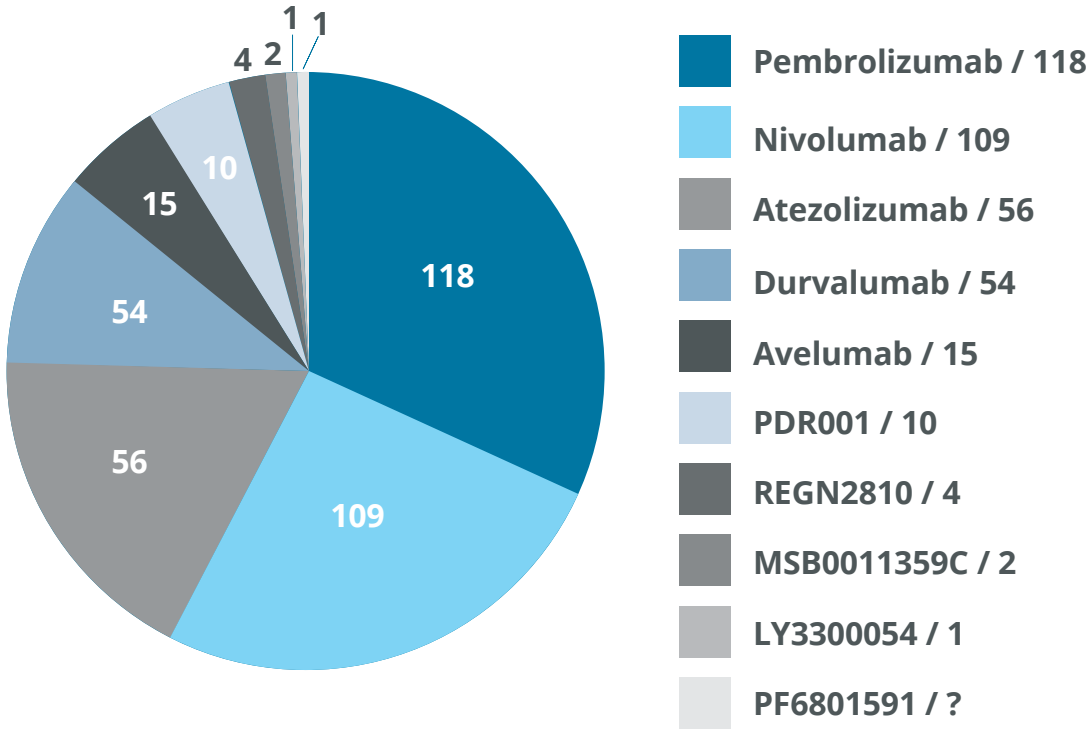
PETER:

I think if you can define the right patient for a non-IO treatment or if a non-IO can deliver better results in certain patient populations, then that's critical for attracting interest in a non-IO asset. Many are combining everything non-IO with the checkpoint inhibitors hoping that something will come out as positive. It will be an evolution. The commercialization of these assets and combinations is probably ahead of the science.

Academic: Lg Pharma PD1/L1 Agent Distribution (Mono and Combo, n=378)



Industry: Lg Pharma PD1/L1 Agent Distribution (Mono and Combo, n=366)



JEFF:

If you're a small biotech, and you have a truly non-IO agent and you have no stratification approach to your story, you're going to be the saddest of the sad. Many of our biotech clients that have what I would call the classical non-IO type of agents are doing what many others are doing, which is a bit of a pivot. Sometimes those pivots or rebrandings have a certain biologic validity to them. There are companies targeting transcription factors or targeting next-generation types of PI3Ks or other TKIs or MTKIs. In this case, the nature of the isoforms that are being hit, or the specific pleiotropic targets that some of those may hit if they're not specific, do result in some direct effects, not only on tumor cell killing, but also on modulation of bad actor immune cells and/or benefit to good actor immune cells. And so, a lot of our clients have agents that can kill tumor cells, but also seem to produce some IO activity and demonstrate some good additivity, if not synergy, with a checkpoint or even a costim. So, biotechs have to develop that story.

PETER:

One potential option for the differentiation of assets, which many small companies are looking at, is the price of the combination. **Can you generate combinations with clinical benefit owning all of the components of the therapy and controlling the price** and thereby making a place for yourself in the market?

> **Can you generate combinations with clinical benefit owning all of the components of the therapy and controlling the price?**

LINDA: **We've talked about understanding patient selection to differentiate your molecule to figure out how to use these non-IO assets in combinations. We looked at the PD-1 battle on biomarkers, but what I hear from you is that, for understanding patient selection, biomarkers are every bit as important, even though the PD-1 story may be a counter example. Is that an accurate statement?**

PETER:

Biomarkers will be extremely important, because understanding these mechanisms tailored to the specific patient and the specific context of the specific target gives the opportunity to create great benefit for those patients. There are many ongoing approaches at a research stage, which will most likely provide better benefit, better patient selection and higher PD-L expression, but we need biomarkers at the diagnosis of the patient.

ERIC:

I think there are a lot of lessons to be learned from the targeted therapy experience of the last ten years. Look at EGFR inhibitors in lung cancer. They were approved with an unselected trial with minimal benefit, and then we identified the groups that truly benefited from them. Then there was a dedication to studying patients over their therapeutic life concerning how tumors change their trajectory and become resistant, and in that way we were able get to second and third generation agents. **That's a good lesson for immuno-oncology—to study which patients are benefiting and how they become resistant.** That helps us become more precise. I do have a little bit of worry concerning how all this IO enthusiasm will affect payments. I'm glad I'm not in the insurance business and have to decide if every patient with advanced cancer is going to get PD-1 antibody as a backbone. I have some sense that if there

really is going to be **a value-based care plan for payers and hospitals, that may force us to figure out which people are going to get major benefits** from the IO antibodies and focus on those patients, while looking for alternative solutions for patients that are not going to see that benefit.

JEFF:

There's no doubt that there's a change coming. It's not going to be business as usual. We have to be thinking about the value

of drugs, individually and in potential combination. And, it's more than just pricing. It's asking: What is this drug and what is the presumptive value of the combination of my drug X with a checkpoint inhibitor? Is that value justified?

That will feed back into whether you have a checkpoint in your pipeline or not. Right now the value of having one is it may give you more flexibility in clinical development, and it may give you more flexibility in terms of pricing out your regimen. That might also be true if it turns out that bispecifics of checkpoints come into play and can do in a single molecule what two checkpoints are able to do. Similarly, adoptive cell therapies, which are complex agents, can be engineered not only to target, but to provide checkpoint inhibition and costims. **Bispecifics and cell therapy may be a way to better address the value proposition of combinations.** I think the point is that while efficacy is paramount, it has to be efficacy in the context of value.

LINDA: Will CD47 inhibitors be as popular as PD-1 inhibitors?

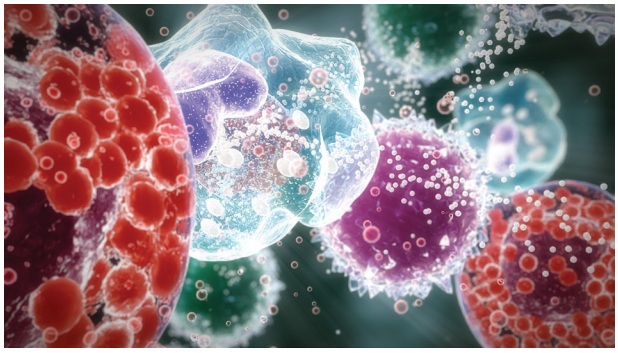
AXEL:

It depends on what they can deliver. PD-1 has delivered. If CD47 can deliver equal value, then yes, they will be, but it's too early to know.

LINDA: What are the most promising investigational immune cell agonists?

AXEL:

OX40 is of interest. There's a lot of OX40 investigation going on. We haven't figured out yet how to dose this agent and how to then find the right patient population for it. There is more work to be done, but mechanistically it makes sense to have an agonist in the portfolio available to patients. We just have to sort out how these things offer their best benefit. This is probably one of the prime examples of how the biomarkers story will influence drug development. We almost didn't need it at all for PD-1, although that's not fully true for PDL-1. We didn't need it for CTLA-4, but **as we dig deeper and look for more specific populations, we will need biomarkers to identify the right patients and the place where the drug can exert its effect**. I'm sure that there will be some costimulatory agonists that will end up being effective and become medicine.



LINDA: Will quantitative tissue immunohistochemistry be a possibility for interpretation for the right context for drug use?

ERIC:

I think that's going to be a very interesting area in a couple of ways. One is multiplex immunohistochemistry, where one can visualize the geography of tumors and how they're involved with immune infiltrative cells of different types. **The more multiplexing we can do, the more questions we can answer**. The other potential is to ignore the landscape or geography but develop protein-based markers almost akin to gene expression profiling, but with proteomic technology. It could be very helpful to be able to look at immune proteins in

a multiplex way from a single needle biopsy in a patient across their therapeutic landscape. We really need to reinvigorate the study of human cancer biology to figure out how we're going to place all these therapeutics. That's what worked for targeted therapy and that's the lesson for immune therapy to avoid a tremendous amount of trials and not understanding why things work and why things don't work.

AXEL:
We get very excited about the science, and we should, but what we're not paying enough attention to is the coordination of the methods we use to investigate these biomarkers. Right now we're not creating apples to apples comparisons across trials and programs, making it extremely hard to make sense of all the data. **Clearly, asset validation and asset harmonization and the sharing of methods across the field will benefit everybody.**

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Clearly, asset validation and asset harmonization and the sharing of methods across the field will benefit everybody.

LINDA: **We heard several big themes. The rapid growth in IO has changed much of the thinking in cancer drug development, but there is still room for many non-IO agents. But the developers of non-IO agents need to really develop the story of patient selection and the context for efficacy. Combinations with checkpoints alone are not sufficient to generate partner interest. Non-IO agents have effects on IO but the understanding of combination, synergy and sequencing is lagging. Biomarkers will be every bit as important in the future despite the early absence of biomarkers in development of the first checkpoint inhibitors.**

About the Panelists

LINDA PULLAN, PHD
PULLAN CONSULTING

Linda offers biotech and pharmaceutical companies consulting in all aspects of partnering. Linda has a Ph.D. in Biochemistry, a B.S. in Chemistry and more than twenty years of drug industry experience. Linda has worked in many deals, from in-licensing to out-licensing and a few acquisitions. Linda publishes a free monthly newsletter, *Pullan's Pieces*.

JEFF BOCKMAN, PHD
VICE PRESIDENT, DEFINED HEALTH

Jeff leads the Oncology and Virology Practices at Defined Health. He received a BA from University of California at San Diego, a PhD in Medical Microbiology from the University of California at Berkeley, and an MA in English/Creative Writing from New York University.

ABOUT AXEL HOOS, MD, PHD
VICE PRESIDENT, ONCOLOGY R&D AND HEAD OF IMMUNO-ONCOLOGY AT GLAXOSMITHKLINE PHARMACEUTICALS (GSK)

Axel builds the immuno-oncology portfolio of GSK across the modalities of antibodies, small molecules, bispecific molecules and cell & gene therapies, for which he directs clinical and discovery research.

PETER SANDOR, MD, MBA
VICE PRESIDENT AND HEAD ONCOLOGY MARKETING STRATEGY, ASTELLAS

Peter Sandor was most recently the Vice President, Global Marketing Oncology at Amgen responsible for the successful realization of the commercial potential for Amgen's oncology assets. Peter has 19 years of progressive marketing experience. Prior to Amgen, he held different positions at Bayer Healthcare, including Head of Strategy and Portfolio Management Specialty Medicine, Commercial Development and Life Cycle Management Global Oncology. He also worked for Berlex Laboratories as the lead of the global launch team for a key oncology compound, and held multiple marketing roles with Schering AG in Germany and Hungary.

ABOUT ERIC HAURA, MD
SENIOR MEMBER, DEPARTMENT OF THORACIC ONCOLOGY, H. LEE MOFFITT CANCER CENTER, TAMPA, FL

Dr. Eric Haura received his BS in biomedical engineering from Johns Hopkins University, completed medical school at Duke University School of Medicine, completed a residency program in internal medicine at Johns Hopkins, and then returned to Duke to pursue a clinical fellowship in hematology and oncology. He is co-leader of the Chemical Biology and Molecular Medicine Program and directs the Lung Cancer Center of Excellence at Moffitt. He is a board certified medical oncologist specialized in the treatment of all types of lung cancers and thoracic cancers. His research interests include assessment of signaling pathways using proteomic technology, chemical biology tools to study drug mechanisms of action, and technologies to enable precision medicine.

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Pandesa Corporation, dba ShareVault
Headquarters
16795 Lark Avenue, Suite 210
Los Gatos, CA 95032

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